

538,141

Rec'd PCT/PTO 08 JUN 2005

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number  
**WO 2004/052930 A2**

- (51) International Patent Classification<sup>7</sup>: **C07K 14/705**, 14/54, 7/08, A61K 39/385, 9/127, 47/48
- (21) International Application Number: PCT/DK2003/000859
- (22) International Filing Date: 11 December 2003 (11.12.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
PA 2002 01893 11 December 2002 (11.12.2002) DK  
60/432,532 11 December 2002 (11.12.2002) US  
PA 2003 00198 12 February 2003 (12.02.2003) DK  
60/446,707 12 February 2003 (12.02.2003) US
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- (72) Inventor; and
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- (74) Agent: INSPICOS A/S; Bøge Allé 3, P.O. Box 45, DK-2970 Hørsholm (DK).
- (81) Designated States (*national*): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, EG, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**  
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TARGETING SINGLE EPITOPES

(57) **Abstract:** The invention relates to novel immunogenic agents that are capable of inducing specific B-cell immunity directed against one single epitope present in a self-antigen. The immunogenic agent is a chimeric binding protein that binds specifically to a first receptor, said first receptor being one that binds a second receptor present in an antigen of an animal, wherein said chimeric binding protein comprises: (a) a B-cell epitope in the form of a binding site that specifically binds the first receptor and which competes with the second receptor for binding to the first receptor, (b) a scaffold protein structure being autologous in said mammal, and (c) at least one tolerance breaking amino acid sequence, which is heterologous in said animal and which binds to an MHC Class II molecule in said animal. In preferred embodiments, the chimeric binding protein is in the form of an anti-idiotypic antibody having a tolerance-breaking amino acid sequence introduced. The invention further relates to methods of preparing the immunogens and methods of using the immunogens in therapy. Also, the invention relates to proteins, nucleic acid fragments, recombinantly modified host cells and virus that are useful in the practice of the methods of the invention.

WO 2004/052930 A2

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PCT

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WO 2004/052930 A3

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14/54, 7/08, A61K 39/385, 9/127, 47/48

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PCT/DK2003/000859

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(74) Agent: INSPICOS A/S; Bøge Allé 3, P.O. Box 45,  
DK-2970 Hørsholm (DK).

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lity model), AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ,  
CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE  
(utility model), DE, DK (utility model), DK, DM, DZ, EC,  
EE (utility model), EE, EG, ES, FI (utility model), FI, GB,  
GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,  
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,  
MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL,  
PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL,  
SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN,  
YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (BW, GH,  
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE,  
SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA,  
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

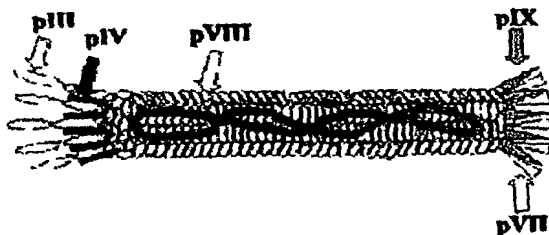
**Published:**

- with international search report
- before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments

(88) Date of publication of the international search report:  
29 July 2004

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
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(57) Abstract: The invention relates to novel immunogenic  
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directed against one single epitope present in a self-antigen.  
The immunogenic agent is a chimeric binding protein that binds  
specifically to a first receptor, said first receptor being one that  
binds a second receptor present in an antigen of an animal, wherein  
said chimeric binding protein comprises: (a) a B-cell epitope in the  
form of a binding site that specifically binds the first receptor and  
which competes with the second receptor for binding to the first  
receptor, (b) a scaffold protein structure being autologous in said

mammal, and (c) at least one tolerance breaking amino acid sequence, which is heterologous in said animal and which binds to an  
MHC Class II molecule in said animal. In preferred embodiments, the chimeric binding protein is in the form of an anti-idiotypic  
antibody having a tolerance-breaking amino acid sequence introduced. The invention further relates to methods of preparing the  
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recombinantly modified host cells and virus that are useful in the practice of the methods of the invention.

WO 2004/052930 A3

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/DK 03/00859

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/705 C07K14/54 C07K7/08 A61K39/385 A61K9/127  
A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	US 2003/228324 A1 (LUND GARRY ET AL) 11 December 2003 (2003-12-11) claim 8	1-56
P,X	WO 03 042244 A (BRATT TOMAS ;KLYSNER STEEN (DK); PHARMEXA AS (DK); VOLDORG BJOERN) 22 May 2003 (2003-05-22) claims 1-48	1-56
X	WO 97 26784 A (ALEXANDER JEFFERY L ;DEFREES SHAWN (US); CYTEL CORP (US); SETTE AL) 31 July 1997 (1997-07-31) claims 1-35	1-56
X	WO 99 58658 A (EPIMMUNE INC) 18 November 1999 (1999-11-18) claim 40	27-31
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 April 2004

Date of mailing of the international search report

17. 05. 2004

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/DK 03/00859

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 41741 A (CELIS ESTEBAN ;SIDNEY JOHN (US); CHESNUT ROBERT (US); EPIMMUNE INC) 14 June 2001 (2001-06-14) claims 1-39; example 7 ---	21
X	LA ROSA CORINNA ET AL: "Preclinical development of an adjuvant-free peptide vaccine with activity against CMV pp65 in HLA transgenic mice." BLOOD. UNITED STATES 15 NOV 2002, vol. 100, no. 10, 15 November 2002 (2002-11-15), pages 3681-3689, XP002277230 ISSN: 0006-4971 table 1 ---	21
A	VOGEL M ET AL: "Mimicry of human IgE epitopes by anti-idiotypic antibodies." JOURNAL OF MOLECULAR BIOLOGY. ENGLAND 19 MAY 2000, vol. 298, no. 5, 19 May 2000 (2000-05-19), pages 729-735, XP002277231 ISSN: 0022-2836 figures 1-5 ---	1-56
A	WEATHINGTON NATHANIEL M ET AL: "Rational design of peptide vaccines for autoimmune disease: harnessing molecular recognition to fix a broken network." EXPERT REVIEW OF VACCINES. ENGLAND FEB 2003, vol. 2, no. 1, February 2003 (2003-02), pages 61-73, XP002277232 ISSN: 1476-0584 figure 3 ---	1-56
P,A	US 2003/185845 A1 (BRATT TOMAS ET AL) 2 October 2003 (2003-10-02) claims 1-48 ---	1-56
A	WO 95 17212 A (CORRADIN GIAMPIETRO ;HEALY FRANK (CH); MACH JEAN PIERRE (CH); BOEH) 29 June 1995 (1995-06-29) claims 1-11 ---	1-56
A	WO 95 05849 A (ELSNER HENRIK ;MOURITSEN & ELSNER A S (DK); MOURITSEN SOEREN (DK)) 2 March 1995 (1995-03-02) claims 1-9 ---	1-56
A	WO 95 07707 A (CYTEL CORP) 23 March 1995 (1995-03-23) claims 1-17 -----	1-56

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 03/00859

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 48-49, 55-56  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: Part of 1-25, 27-33, 35-36, 38-47, 50-54  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☒ Claims Nos.: 26, 34, 37  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/ DK 03/ 00859

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 48-49, 55-56

Claims 48-49 and 55-56 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

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Continuation of Box I.2

Claims Nos.: Part of 1-25,27-33,35-36,38-47,50-54

Part of present claims 1-25, 27-33, 35-36, 38-47, 50-54 relate to proteins, vectors, cells, compositions and methods defined by reference to desirable characteristics or properties of a "chimeric binding protein", which comprises three parts, namely:

- a- Epitope (B-cell), that binds specifically and/or competitively,
- b- Scaffold protein structure, that stabilizes the 3D conformation,
- c- At least one "tolerance breaking amino acid sequence", that binds to an MHC class II molecule.

The claims cover all possible proteins, vectors, cells, compositions and methods having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of such proteins, vectors, cells, compositions and methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the proteins, vectors, cells, compositions and methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the proteins, vectors, cells, compositions and methods, those prepared in example 1 (only example) and part of claim 21 (part of sequences C.tetani/Padre).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/ DK 03/00859

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/DK 03/00859

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